

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 08 December 2000 (08.12.00)	Applicant's or agent's file reference IPD/P1234/WOD
International application No. PCT/GB00/01104	Priority date (day/month/year) 24 March 1999 (24.03.99)
International filing date (day/month/year) 23 March 2000 (23.03.00)	
Applicant ALPAR, Hazire, Oya et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

12 October 2000 (12.10.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia TEFY

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

SKELTON, Stephen, Richard
D/IPR Formalities Section
Poplar 2
MOD Abbey Wood #19
P.O. Box 702
Bristol BS34 8JH
ROYAUME-UNI

Date of mailing (day/month/year) 03 août 2001 (03.08.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference IPD/P1234/WOD	
International application No. PCT/GB00/01104	International filing date (day/month/year) 23 mars 2000 (23.03.00)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

THE SECRETARY OF STATE FOR DEFENCE
Defence Evaluation and Research
Agency
Ively Road
Farnborough
Hampshire GU14 0LX
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

THE SECRETARY OF STATE FOR DEFENCE
DSTL
Porton Down
Salisbury
Wiltshire SP4 0JQ
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>Maria Victoria CORTIELLO</p> <p>Telephone No.: (41-22) 338.83.38</p>
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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 September 2000 (28.09.2000)

PCT

(10) International Publication Number
WO 00/56361 A3

- (51) International Patent Classification⁷: **A61K 39/39**, 39/02, 9/16, 9/51, A61P 31/04
- (74) Agent: **BOWDERY, A., O.**; D/IPR, Formalities Section, Poplar 2, MOD Abbey Wood #19, Bristol BS34 8JH (GB).
- (21) International Application Number: **PCT/GB00/01104**
- (22) International Filing Date: **23 March 2000 (23.03.2000)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
9906694.6 24 March 1999 (24.03.1999) GB
9906696.1 24 March 1999 (24.03.1999) GB
- (71) Applicant (for all designated States except US): **THE SECRETARY OF STATE FOR DEFENCE [GB/GB]**; Defence Evaluation and Research Agency, Ively Road, Farnborough, Hampshire GU14 0LX (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **ALPAR, Hazire, Oya [GB/GB]**; Aston University, Aston Triangle, Birmingham B4 7ET (GB). **SOMAVARAPU, Satyanarayana [IN/GB]**; Aston University, Aston Triangle, Birmingham B4 7ET (GB). **WILLIAMSON, Ethel, Diane [GB/GB]**; CBD Porton Down, Salisbury, Wiltshire SP4 0JQ (GB). **BAILLIE, Leslie, William, James [GB/GB]**; CBD Porton Down, Salisbury, Wiltshire SP4 0JQ (GB).
- (81) Designated States (national): **AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**
- (84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**
- Published:
— With international search report.
- (88) Date of publication of the international search report:
1 March 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **VACCINE COMPOSITION**

(57) Abstract: A pharmaceutical composition comprising: (i) a biologically active agent; (ii) an adjuvant chemical which increases the effect of the biologically active agent, said chemical selected from one or more of: A) a polyamino acid, B) a vitamin or vitamin derivative, C) cationic pluronics, D) a clathrate, E) a complexing agent, F) cetrimides, G) an S-layer protein, or H) methyl-glucamine; (iii) a pharmaceutically acceptable carrier or diluent, provided that when the chemical (ii) above is selected from D) or E), the biologically active agent is an agent which is capable of generating a protective immune response in an animal to which it is administered. The composition, which may be in the form of a solution or particles such as microspheres or liposomes, is particularly useful for mucosal administration of vaccines especially by the intra-nasal route or by parenteral routes.

WO 00/56361 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01104

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/39 A61K39/02 A61K9/16 A61K9/51 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, PAJ, WPI Data, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 290 141 A (WELLCOME FOUNDATION) 20 September 1972 (1972-09-20) the whole document	1-5, 12, 15, 24, 25
X	FR 2 306 684 A (LABORATOIRES CRINEX) 5 November 1976 (1976-11-05) the whole document	1-5, 12, 15, 24, 25
X	US 5 650 155 A (LAMMERT C. ET AL.) 22 July 1997 (1997-07-22) the whole document	1-5, 12, 15, 24, 25
X	US 5 562 910 A (DAYNES R.A. ET AL.) 8 October 1996 (1996-10-08) the whole document	1-5, 12, 15, 24, 25

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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 October 2000

Date of mailing of the international search report

26/10/2000

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Moreau, J

INTERNATIONAL SEARCH REPORT

Int. Patent Application No

PCT/GB 00/01104

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 20070 A (SECRETECH) 15 September 1994 (1994-09-15) the whole document ----	1-5, 12, 15, 24, 25
X	EP 0 283 085 A (AKZO) 21 September 1988 (1988-09-21) the whole document ----	1-5, 12, 15, 24, 25
X	DE 196 03 649 A (LUBITZ W. ET AL.) 7 August 1997 (1997-08-07) the whole document ----	1-5, 12, 15, 24, 25
A	JAHN-SCHMID B ET AL: "Immunoreactivity of allergen (Bet v 1) conjugated to crystalline bacterial cell surface layers (S-layers)" IMMUNOTECHNOLOGY, NL, ELSEVIER SCIENCE PUBLISHERS BV, vol. 2, no. 2, 1 June 1996 (1996-06-01), pages 103-113, XP004052675 ISSN: 1380-2933 the whole document ----	1-25
A	EYLES J E ET AL: "Intra nasal administration of poly-lactic acid microsphere co-encapsulated Yersinia pestis subunits confers protection from pneumonic plague in the mouse" VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 7, 1 April 1998 (1998-04-01), pages 698-707, XP004112258 ISSN: 0264-410X the whole document ----	1-25
A	MCBRIDE B W ET AL: "Protective efficacy of a recombinant protective antigen against Bacillus anthracis challenge and assessment of immunological markers" VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 8, 1 May 1998 (1998-05-01), pages 810-817, XP004118489 ISSN: 0264-410X the whole document ----- -/-	1-25

INTERNATIONAL SEARCH REPORT

Im  al Application No

PCT/GB 00/01104

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p> GRIFFIN K F ET AL: "Immune responses to V antigen of Yersinia pestis co-encapsulated with IFN-gamma: effect of dose and formulation" VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 5, 1 March 1998 (1998-03-01), pages 517-521, XP004106965 ISSN: 0264-410X the whole document ----- </p>	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/GB 00/01104

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
GB 1290141	A	20-09-1972	NONE		
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Patent Application No

PCT/GB 00/01104

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9420070	A		CA 2158040 A	15-09-1994
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			GR 3007039 T	30-07-1993
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			JP 2562827 B	11-12-1996
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			US 5026543 A	25-06-1991
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			ZA 8801694 A	06-09-1988
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			WO 9728263 A	07-08-1997
			EP 0882129 A	09-12-1998
			JP 2000503850 T	04-04-2000
			NZ 331300 A	29-06-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference IPD/P1234/WOD	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/GB 00/ 01104	International filing date (day/month/year) 23/03/2000	(Earliest) Priority Date (day/month/year) 24/03/1999
Applicant THE SECRETARY OF STATE FOR DEFENCE et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

☒ **None of the figures.**

INTERNATIONAL SEARCH REPORT

International Application No

P 00/01104

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/39 A61K39/02 A61K9/16 A61K9/51 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, PAJ, WPI Data, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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3 X	US 5 650 155 A (LAMMERT C. ET AL.) 22 July 1997 (1997-07-22) the whole document ---	1-5, 12, 15, 24, 25
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 October 2000

Date of mailing of the international search report

26/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Moreau, J

INTERNATIONAL SEARCH REPORT

International Application No

P GB 00/01104

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
5 X	WO 94 20070 A (SECRETECH) 15 September 1994 (1994-09-15) the whole document ---	1-5, 12, 15, 24, 25
7 X	EP 0 283 085 A (AKZO) 21 September 1988 (1988-09-21) the whole document ---	1-5, 12, 15, 24, 25
7 X	DE 196 03 649 A (LUBITZ W. ET AL.) 7 August 1997 (1997-08-07) the whole document ---	1-5, 12, 15, 24, 25
A	JAHN-SCHMID B ET AL: "Immunoreactivity of allergen (Bet v 1) conjugated to crystalline bacterial cell surface layers (S-layers)" IMMUNOTECHNOLOGY, NL, ELSEVIER SCIENCE PUBLISHERS BV, vol. 2, no. 2, 1 June 1996 (1996-06-01), pages 103-113, XP004052675 ISSN: 1380-2933 the whole document ---	1-25
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A	MCBRIDE B W ET AL: "Protective efficacy of a recombinant protective antigen against Bacillus anthracis challenge and assessment of immunological markers" VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 8, 1 May 1998 (1998-05-01), pages 810-817, XP004118489 ISSN: 0264-410X the whole document --- -/--	1-25

INTERNATIONAL SEARCH REPORT

International Application No

P GB 00/01104

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>GRIFFIN K F ET AL: "Immune responses to V antigen of Yersinia pestis co-encapsulated with IFN-gamma: effect of dose and formulation" VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 5, 1 March 1998 (1998-03-01), pages 517-521, XP004106965 ISSN: 0264-410X the whole document -----</p>	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/01104

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 1290141	A	20-09-1972	NONE	
FR 2306684	A	05-11-1976	NONE	
US 5650155	A	22-07-1997	US 5667784 A	16-09-1997
			AT 115862 T	15-01-1995
			AU 633043 B	21-01-1993
			AU 4897590 A	09-08-1990
			CA 2008856 A	04-08-1990
			CN 1044594 A, B	15-08-1990
			DE 69015222 D	02-02-1995
			DE 69015222 T	04-05-1995
			DK 382271 T	01-05-1995
			EP 0382271 A	16-08-1990
			ES 2068989 T	01-05-1995
			GR 3015438 T	30-06-1995
			HU 56285 A, B	28-08-1991
			JP 2250835 A	08-10-1990
			JP 2892739 B	17-05-1999
			KR 162646 B	01-12-1998
			NZ 232354 A	25-09-1991
			ZA 9000512 A	28-11-1990
US 5562910	A	08-10-1996	US 5837269 A	17-11-1998
			AU 679215 B	26-06-1997
			AU 6234894 A	29-08-1994
			CA 2153794 A	18-08-1994
			CZ 9501975 A	13-12-1995
			EP 0686042 A	13-12-1995
			FI 953608 A	19-09-1995
			HU 72404 A	29-04-1996
			JP 8508718 T	17-09-1996
			NO 953049 A	03-10-1995
			NZ 262597 A	24-10-1997
			PL 310112 A	27-11-1995
			SK 97395 A	08-05-1996
			WO 9417823 A	18-08-1994
			US 5518725 A	21-05-1996
			US 5824313 A	20-10-1998
			US 5753237 A	19-05-1998
			US 5919465 A	06-07-1999
			AT 192651 T	15-05-2000
			AU 652130 B	18-08-1994
			AU 6501990 A	18-04-1991
			AU 667018 B	29-02-1996
			AU 7572794 A	08-12-1994
			CA 2066716 A	26-03-1991
			DE 69033541 D	15-06-2000
			EP 0494224 A	15-07-1992
			JP 2505313 B	05-06-1996
			JP 5502856 T	20-05-1993
			US 5540919 A	30-07-1996
			WO 9104030 A	04-04-1991
			US 5827841 A	27-10-1998
WO 9420070	A	15-09-1994	AU 692440 B	11-06-1998
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01104

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9420070 A		CA 2158040 A	15-09-1994
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		JP 2000503850 T	04-04-2000
		NZ 331300 A	29-06-1999

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BOWDERY, A.O.
D/IPR Formalities Section
Poplar 2 MOD Abbey Wood 19
Bristol BS34 8JH
GRANDE BRETAGNE

IPR1 RECEIVED

11 JUL 2001

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

09.07.2001

Applicant's or agent's file reference
P1234/WOD

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/01104

International filing date (day/month/year)
23/03/2000

Priority date (day/month/year)
24/03/1999

Applicant

THE SECRETARY OF STATE FOR DEFENCE et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

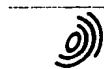
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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D-80298 Munich
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Authorized officer



Neumann, M

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PATENT COOPERATION TREATY
PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1234/WOD		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01104	International filing date (day/month/year) 23/03/2000	Priority date (day/month/year) 24/03/1999	
International Patent Classification (IPC) or national classification and IPC A61K39/39			
Applicant THE SECRETARY OF STATE FOR DEFENCE et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 6 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input checked="" type="checkbox"/> Certain defects in the international applicationVIII <input checked="" type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 12/10/2000		Date of completion of this report 09.07.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Weijland, A Telephone No. +49 89 2399 7490 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01104

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-14,16-20	as originally filed			
15	as received on	17/04/2001	with letter of	17/04/2001

Claims, No.:

1-25	as received on	17/04/2001	with letter of	17/04/2001
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Drawings, sheets:

1/8-8/8	as originally filed
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2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/01104

- ☐ the description, pages:
☒ the claims, Nos.: 1,24,25
☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 15-17, 24 (with respect to industrial applicability).

because:

- ☒ the said international application, or the said claims Nos. 15-17,24 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01104

1. Statement

Novelty (N)	Yes:	Claims	9,11
	No:	Claims	1-8,10,12-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-14, 18-23,25
	No:	Claims	

2. Citations and explanations **see separate sheet**

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/01104

The following documents (D) are referred to in this opinion; the numbering will be adhered to the rest of the procedure:

- D1: GB-A-1 290 141 (WELLCOME FOUNDATION) 20 September 1972 (1972-09-20)
- D2: FR-A-2 306 684 (LABORATOIRES CRINEX) 5 November 1976 (1976-11-05)
- D3: US-A-5 650 155 (LAMMERT C. ET AL.) 22 July 1997 (1997-07-22)
- D4: US-A-5 562 910 (DAYNES R.A. ET AL.) 8 October 1996 (1996-10-08)
- D5: WO 94 20070 A (SECRETECH) 15 September 1994 (1994-09-15)
- D6: EP-A-0 283 085 (AKZO) 21 September 1988 (1988-09-21)
- D7: DE 196 03 649 A (LUBITZ W. ET AL.) 7 August 1997 (1997-08-07)
- D8: JAHN-SCHMID B ET AL: 'Immunoreactivity of allergen (Bet v 1) conjugated to crystalline bacterial cell surface layers (S-layers)' IMMUNOTECHNOLOGY, NL, ELSEVIER SCIENCE PUBLISHERS BV, vol. 2, no. 2, 1 June 1996 (1996-06-01), pages 103-113
- D9: EYLES J E ET AL: 'Intra nasal administration of poly-lactic acid microsphere co-encapsulated Yersinia pestis subunits confers protection from pneumonic plague in the mouse' VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 7, 1 April 1998 (1998-04-01), pages 698-707
- D10: GRIFFIN K F ET AL: 'Immune responses to V antigen of Yersinia pestis co-encapsulated with IFN-gamma: effect of dose and formulation' VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 5, 1 March 1998 (1998-03-01), pages 517-521

SECTION I

1. A disclaimer, an element defined by technical features, may be expressly excluded from the protection claimed in order to meet the requirements of novelty. In order for a disclaimer to meet the requirements of Article 34(2)(b) PCT, either (1) the scope of the non-disclaimed subject matter must be explicitly disclosed in the application as filed or (2) the scope of the disclaimer should encompass precisely the disclaimed prior art.

The passages "the composition does not contain a polyacrylic acid" in amended

claim 1 or "the compound is used in the absence of a polyacrylic acid" in amended claims 24 and 25 filed with the letter of 17.04.2001 are not disclosed in the application as filed and do not meet the criteria under (1) above. The disclaimer does, however, encompass the disclosure of D6 and is intended to establish novelty over this document. As this document, however, the closest prior art for the purpose of inventive step of claims 1, 24 and 25 and a disclaimer of a prior art disclosure can be used to establish novelty only, and not inventive step, disclaiming the content of D6 is not acceptable, and the does not meet the requirements of Article 34(2)(b) PCT.

Therefore, this report is based as if these amendments had not been made.

SECTION III

2. Claims 15-17, 24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

3. Novelty (Article 33(2) PCT)

- 3.1 D2 to D4 cited in the International Search Report as document of particular relevance are not pertinent to the present set of claims, since said claims are restricted to water soluble vitamins.

- 3.2 The subject matter of claims 1-8, 10, 12-25 is not novel.

Claims 1-4, 13, 24, 25 are anticipated by D1. D1 (column 1, lines 12-39; column 4, lines 90-100; example 7; claims 1 and 4) discloses base rich polypeptides such as polyornithine ("poly-ornithine" according to present claim 4) as adjuvants in vaccines ("a polyamino acid" according to present claim 1) beside antigens ("biologically active agent" according to present claim 1 or "use of a polyamino acid as immunostimulant" according to present claim 24) to obtain the required

level of protection. Where a first adjuvant is not adequate an additional adjuvant may be used ("further adjuvant" according to present claim 13) in methods for inducing immunity by administering a vaccine ("use of a polyamino acid as immunostimulant in production of a vaccine for use in therapeutic treatment" according to present claim 25). The preparation of a toxoid in physiological saline with poly-L-lysine is described ("the composition is for administration to a mucosal surface" according to present claim 1).

Claims 1-6, 15-17, 24 are anticipated by D5. D5 (claims 1, 4, 8; page 7, second paragraph; page 9, second paragraph; page 10, fourth paragraph) describes an **immunization composition** which comprises, beside antigen ("biologically active agent" according to present claim 1), a mucoadhesive, i.e by interaction of charged groups it binds to the negatively charged mucin, ("cationic pluronics" according to present claims 1,24) and a suitable adjuvant such as a liposome ("carrier or liposome" according to present claims 1 and 6) in an amount sufficient to **induce or enhance** immune response to the antigen. Also a method is disclosed for administering the composition to the animal intranasally ("mucosal...intranasal surface" according present claim 17).

Claims 1-6 are anticipated by D6. D6 (abstract; page 2, last paragraph; page 3, lines 32-35) describes oil free vaccines, that contain block polymers ("cationic pluronics" according to present claim 1) and low molecular weight fractions of pathogens that may be bonded to a carrier such as a liposome ("carrier or liposome" according to present claims 1 and 6) to increase the immunogenicity.

Microspheres are broadly defined on page 8 (lines 14-19) of the present description as consisting of polymeric materials.

Claims 1-3, 5-7, 18-23 are anticipated by D8. D8 (abstract; Table 2; page 112, right column, first paragraph) describes surface S-layers ("S-layer protein" according to present claim 1) as adjuvants for haptens and suggest that they can be suitable carriers for new immunotherapeutic vaccines. rBet v1 ("biologically active agent" according to present claim 1) alone did not induce immune responses, only conjugates of rBet v 1-S-layers ("a microsphere wherein one or more agents are linked to the S-layer protein" according to present claim 21 or

"pharmaceutical composition" according to present claim 23) elicited significant allergen-specific T-cell responses.

Claims 1-3, 5-8,10,12 and 14 are anticipated by D9. D9 (abstract) describes co-encapsulated antigens of F1 and V subunits antigens ("biologically active agent" according to present claim 1) of Yersinia pestis to immunize mice intranasally ("mucosal surface" according to present claims 12). In an animal model protective immunity is obtained provided that the vaccines are micro encapsulated ("first polymeric material" according to present claim 14) with a strong mucosal adjuvant such as the cholera toxin B ("a polyamino acid" or "second polymeric material" according to present claims 1 and 14 respectively) subunit. Thus, intranasal administration of poly-lactic microsphere co-encapsulated ("carrier" or "microsphere comprises poly-(L-lactide)" according to present claims 1 and 10) Yersinia pestis subunits confers protection from pneumonic plague in the mouse.

Claims 1-3, 5-8,10, 12 are anticipated by D10. D10 (abstract) describes induction of immune responses after inoculation of poly(L)lactide microspheres ("carrier" or "microsphere comprises poly-(L-lactide)" according to present claims 1 and 10) containing the V antigen ("biologically active agent" according to present claim 1) of Yersinia pestis and IFN- γ ("a polyamino acid" according to present claim 1). This led to antigen specific immune responses.

Claim 1 differs from D7 in that it describes a pharmaceutical composition comprising the components mentioned under (i), (ii), (iii).

- 3.3 The subject matter of claims 9 and 11 is not disclosed in the prior art documents and is therefore novel.
4. Inventive Step (Article 33(3) PCT).

Dependent claims 9 and 11 do not contain any features which, in combination with the features of claim 1 to which they refer, meet the requirements of the PCT in respect of inventive step, since they are mere alternatives from which the skilled person would choose, without resulting in any unexpected effect whatsoever.

5. The passages in claim 15 "a method of protecting a mammal against infection, which method comprises administration of a composition.." and "the use of a chemical...as an immunostimulant" in claim 24 are considered to cover treatment by therapy and therefore are *in vivo* methods of treatment. Moreover, claim 25 is formulated as a second medical use claim.

For the assessment of the present claims 15-17, 24 and 25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VII

6. Claim 13 is not grouped to claim 2 to which it refers and this contravenes Rule 6.4(c) PCT.
7. The references to the Figures on page 17, lines 11 and 29 of the description do not correspond to the Figures.

SECTION VIII

8. The applicant attributes to the term "biologically active agent" a special meaning, which was not generally known in the technical field concerned at the relevant filing date and contravenes the requirement that the meaning needs to be clear from the wording of the claim alone (the Guidelines C-III 4.2, Article 6 PCT).

15

Preferred compositions of the inventions are vaccine compositions. Thus, in a further aspect, the invention provides a method of protecting a mammal against infection, which method comprises administration of a vaccine composition as described
5 above in particular to a mucosal surface, such as a nasal surface, of a mammal.

The applicants have demonstrated that it is possible to protect experimental animals from inhalation challenge with various
10 pathogens including diphtheria, tetanus and *Y. pestis* through i.n. administration of a combined sub-unit vaccine. The adjuvantisation of these sub-units is advantageous in increasing the immune response as is microencapsulation of the sub-units in accordance with the invention. The high molecular weight
15 polymer utilised in the compositions of the invention appears to be particularly well suited to intra-nasal delivery.

In a further aspect, the invention provides the use of an adjuvant chemical as defined above as an immunostimulant in the
20 production of a vaccine for use in prophylactic or therapeutic treatment.

The invention will now be particularly described by way of example with reference to the accompanying drawings in which:

25 Figures 3 illustrates the specific serum antibody responses following a single nasal application of 1µg V and 5µg F1 antigens of *Yersinia pestis* in compositions according to the invention:

30 Figures 1, 2 and 4 illustrates the immune response to nasally delivered tetanus toxoid (TT) using compositions according to the invention where BS is glycodeoxycholic acid, CYC is dimethyl β cyclodextrin, and VET is Vitamin E TPGS and PO is
35 polyornithine;

Claims

1. A pharmaceutical composition comprising
 - (i) a biologically active agent;
 - 5 (ii) an adjuvant chemical which increases the effect of the biologically active agent, said chemical selected from one or more of:
 - A) a polyamino acid,
 - B) a water soluble vitamin or vitamin derivative,
 - 10 C) positively charged cationic pluronics,
 - D) a clathrate,
 - E) a complexing agent,
 - F) cetrimides;
 - G) an S-layer protein
 - 15 H) Methyl-glucamine; and
 - (iii) a pharmaceutically acceptable carrier or diluent, subject to the following provisos
 - a) when the chemical (ii) above is selected from D) or E), the biologically active agent is an agent which is capable of
20 generating a protective immune response in an animal to which it is administered;
 - b) when the chemical (ii) above is selected from A) and the biologically active agent is an agent which is capable of generating a protective immune response in an animal to which it
25 is administered, the composition is for administration to a mucosal surface,
 - c) when the chemical (ii) above is selected from C) and the biologically active agent is an agent which is capable of generating a protective immune response in an animal to which it
30 is administered, the composition does not contain a polyacrylic acid, and
 - d) where the chemical (ii) above is selected from G) and the biologically active agent is an agent which is capable of generating a protective immune response in an animal to which it
35 is administered, the carrier or diluent of (iii) is a microsphere or liposome.

2. A composition according to claim 1 wherein biologically active agent is an agent that is capable of generating a protective immune response in an animal to which it is administered.

5

3. A composition according to claim 1 or claim 2 wherein the said adjuvant chemical can act as an immunostimulant.

4. A composition according to any one of the preceding claims wherein the said adjuvant chemical is selected from one or more of;

- 10 A) poly-ornithine, for example of molecular weight from 5 to 150kDa;
- B) water soluble vitamins or vitamin derivatives such as vitamin E TPGS (d-alpha tocophenyl polyethylene glycol 1000 succinate),
- 15 C) cationic pluronics which are block copolymers or surfactants which are positively charged, in particular with NH_2^+ groups
- D) complexing agents which form complexes with fatty acids such as deoxycholic acid, or
- 20 E) cyclodextrins and their derivatives such as dimethyl β cyclodextrin.

5. A composition according to any one of the preceding claims wherein the carrier comprises a particle.

25

6. A composition according to claim 5 wherein the particle is a microsphere or liposome.

7. A composition according to claim 6 which comprises a microsphere.

30

8. A composition according to claim 7 wherein the microsphere is prepared using a high molecular weight polymer.

9. A composition according to claim 8 wherein the polymer has a molecular weight of 100kDa or more.

35

10. A composition according to any one of claims 7 to 9 wherein the microsphere comprises poly-(L-lactide).
11. A composition according to any one of the preceding claims
5 wherein the ratio of the chemical (ii) to the carrier is from 99:1 to 9:1 w/w.
12. A composition according to any one of the preceding claims which is adapted for administration to a mucosal surface or is
10 suitable for parenteral administration.
13. A composition according to claim 2 which further comprises a further adjuvant.
14. A method of producing a prophylactic or therapeutic
15 vaccine, which method comprises encapsulating a polypeptide which is capable of producing a protective immune response in a first polymeric material which has a high molecular weight, in the presence of a second polymeric material which increases the
20 biological effect of the composition.
15. A method of protecting a mammal against infection, which method comprises administration of a composition according to any one of claims 1 to 13 to a mammal.
25
16. A method according to claim 15 wherein the composition is applied to a mucosal surface.
17. A method according to claim 16 wherein the mucosal surface
30 comprises an intranasal surface.
18. A microsphere comprising a polymeric carrier and an S-layer protein.
19. A microsphere according to claim 18 wherein said S-layer
35 protein is coated on the surface of the microsphere.

20. A microsphere according to claim 18 or claim 19 which further comprises an agent that is capable of generating a protective immune response in an animal to which it is administered.

5

21. A microsphere according to claim 20 wherein one or more of said agents are linked to the S-layer protein.

22. A pharmaceutical composition comprising a microsphere
10 according to any one of claims 19 to 22.

23. A pharmaceutical composition according to claim 22 wherein said composition is a vaccine, intended to produce a protective immune response against a bacterium, and said S-layer protein is
15 derived from said bacterium.

24. The use of a chemical selected from
A) a polyamino acid,
B) a water soluble vitamin or vitamin derivative,
20 C) positively charged cationic pluronics,
D) a clathrate,
E) a complexing agent,
F) cetrinides;
G) an S-layer protein; or
25 H) Methyl-glucamine

as an immunostimulant, provided that in the case of A), the immunostimulant is applied to a mucosal surface, in the case of C, the compound is used in the absence of a polyacrylic acid.

30 25. The use of an adjuvant chemical selected from
A) a polyamino acid,
B) a water soluble vitamin or vitamin derivative,
C) positively charged cationic pluronics,
D) a clathrate,
35 E) a complexing agent,
F) cetrinides;
G) an S-layer protein; or
H) Methyl-glucamine

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as an immunostimulant in the production of a vaccine for use in prophylactic or therapeutic treatment, provided that in the case of A), the immunostimulant is used in a vaccine which is applied to a mucosal surface, and in the case of C), the compound is used
5 in the absence of a polyacrylic acid.

Empfangszeit 17. Apr. 16:22

AMENDED SHEET

REC'D 11 JUL 2001


WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

13

Applicant's or agent's file reference P1234/WOD	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01104	International filing date (day/month/year) 23/03/2000	Priority date (day/month/year) 24/03/1999
International Patent Classification (IPC) or national classification and IPC A61K39/39		
Applicant THE SECRETARY OF STATE FOR DEFENCE et al.		
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<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input checked="" type="checkbox"/> Certain defects in the international application</p> <p>VIII <input checked="" type="checkbox"/> Certain observations on the international application</p>		
Date of submission of the demand 12/10/2000	Date of completion of this report 09.07.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Weijland, A Telephone No. +49 89 2399 7490	



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01104

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

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Claims, No.:

1-25	as received on	17/04/2001	with letter of	17/04/2001
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Drawings, sheets:

1/8-8/8	as originally filed
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2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

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EXAMINATION REPORT**

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- ☐ the description, pages:
☒ the claims, Nos.: 1,24,25
☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 15-17, 24 (with respect to industrial applicability).

because:

- ☒ the said international application, or the said claims Nos. 15-17,24 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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1. Statement

Novelty (N)	Yes:	Claims	9,11
	No:	Claims	1-8,10,12-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-14, 18-23,25
	No:	Claims	

2. Citations and explanations **see separate sheet**

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

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The following documents (D) are referred to in this opinion; the numbering will be adhered to the rest of the procedure:

- D1: GB-A-1 290 141 (WELLCOME FOUNDATION) 20 September 1972 (1972-09-20)
- D2: FR-A-2 306 684 (LABORATOIRES CRINEX) 5 November 1976 (1976-11-05)
- D3: US-A-5 650 155 (LAMMERT C. ET AL.) 22 July 1997 (1997-07-22)
- D4: US-A-5 562 910 (DAYNES R.A. ET AL.) 8 October 1996 (1996-10-08)
- D5: WO 94 20070 A (SECRETECH) 15 September 1994 (1994-09-15)
- D6: EP-A-0 283 085 (AKZO) 21 September 1988 (1988-09-21)
- D7: DE 196 03 649 A (LUBITZ W.ET AL.) 7 August 1997 (1997-08-07)
- D8: JAHN-SCHMID B ET AL: 'Immunoreactivity of allergen (Bet v 1) conjugated to crystalline bacterial cell surface layers (S-layers)'
IMMUNOTECHNOLOGY,NL,ELSEVIER SCIENCE PUBLISHERS BV, vol. 2, no. 2, 1 June 1996 (1996-06-01), pages 103-113
- D9: EYLES J E ET AL: 'Intra nasal administration of poly-lactic acid microsphere co-encapsulated Yersinia pestis subunits confers protection from pneumonic plague in the mouse' VACCINE,GB,BUTTERWORTH SCIENTIFIC.
GUILDFORD, vol. 16, no. 7, 1 April 1998 (1998-04-01), pages 698-707
- D10: GRIFFIN K F ET AL: 'Immune responses to V antigen of Yersinia pestis co-encapsulated with IFN-gamma: effect of dose and formulation'
VACCINE,GB,BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 5, 1 March 1998 (1998-03-01), pages 517-521

SECTION I

1. A disclaimer, an element defined by technical features, may be expressly excluded from the protection claimed in order to meet the requirements of novelty. In order for a disclaimer to meet the requirements of Article 34(2)(b) PCT, either (1) the scope of the non-disclaimed subject matter must be explicitly disclosed in the application as filed or (2) the scope of the disclaimer should encompass precisely the disclaimed prior art.

The passages "the composition does not contain a polyacrylic acid" in amended

claim 1 or "the compound is used in the absence of a polyacrylic acid" in amended claims 24 and 25 filed with the letter of 17.04.2001 are not disclosed in the application as filed and do not meet the criteria under (1) above. The disclaimer does, however, encompass the disclosure of D6 and is intended to establish novelty over this document. As this document, however, the closest prior art for the purpose of inventive step of claims 1, 24 and 25 and a disclaimer of a prior art disclosure can be used to establish novelty only, and not inventive step, disclaiming the content of D6 is not acceptable, and the does not meet the requirements of Article 34(2)(b) PCT.

Therefore, this report is based as if these amendments had not been made.

SECTION III

2. Claims 15-17, 24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

3. Novelty (Article 33(2) PCT)
 - 3.1 D2 to D4 cited in the International Search Report as document of particular relevance are not pertinent to the present set of claims, since said claims are restricted to water soluble vitamins.
 - 3.2 The subject matter of claims 1-8, 10,12-25 is not novel.

Claims 1-4, 13, 24, 25 are anticipated by D1. D1 (column 1, lines 12-39; column 4, lines 90-100; example 7; claims 1 and 4) discloses base rich polypeptides such as polyornithine ("poly-ornithine" according to present claim 4) as adjuvants in vaccines ("a polyamino acid" according to present claim 1) beside antigens ("biologically active agent" according to present claim 1 or "use of a polyamino acid as immunostimulant" according to present claim 24) to obtain the required

level of protection. Where a first adjuvant is not adequate an additional adjuvant may be used ("further adjuvant" according to present claim 13) in methods for inducing immunity by administering a vaccine ("use of a polyamino acid as immunostimulant in production of a vaccine for use in therapeutic treatment" according to present claim 25). The preparation of a toxoid in physiological saline with poly-L-lysine is described ("the composition is for administration to a mucosal surface" according to present claim 1).

Claims 1-6, 15-17, 24 are anticipated by D5. D5 (claims 1, 4, 8; page 7, second paragraph; page 9, second paragraph; page 10, fourth paragraph) describes an **immunization composition** which comprises, beside antigen ("biologically active agent" according to present claim 1), a mucoadhesive, i.e by interaction of charged groups it binds to the negatively charged mucin, ("cationic pluronics" according to present claims 1,24) and a suitable adjuvant such as a liposome ("carrier or liposome" according to present claims 1 and 6) in an amount sufficient to **induce or enhance** immune response to the antigen. Also a method is disclosed for administering the composition to the animal intranasally ("mucosal...intranasal surface" according present claim 17).

Claims 1-6 are anticipated by D6. D6 (abstract; page 2, last paragraph; page 3, lines 32-35) describes oil free vaccines, that contain block polymers ("cationic pluronics" according to present claim 1) and low molecular weight fractions of pathogens that may be bonded to a carrier such as a liposome ("carrier or liposome" according to present claims 1 and 6) to increase the immunogenicity.

Microspheres are broadly defined on page 8 (lines 14-19) of the present description as consisting of polymeric materials.

Claims 1-3, 5-7, 18-23 are anticipated by D8. D8 (abstract; Table 2; page 112, right column, first paragraph) describes surface S-layers ("S-layer protein" according to present claim 1) as adjuvants for haptens and suggest that they can be suitable carriers for new immunotherapeutic vaccines. rBet v1 ("biologically active agent" according to present claim 1) alone did not induce immune responses, only conjugates of rBet v 1-S-layers ("a microsphere wherein one or more agents are linked to the S-layer protein" according to present claim 21 or

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"pharmaceutical composition" according to present claim 23) elicited significant allergen-specific T-cell responses.

Claims 1-3, 5-8, 10, 12 and 14 are anticipated by D9. D9 (abstract) describes co-encapsulated antigens of F1 and V subunits antigens ("biologically active agent" according to present claim 1) of Yersinia pestis to immunize mice intranasally ("mucosal surface" according to present claims 12). In an animal model protective immunity is obtained provided that the vaccines are micro encapsulated ("first polymeric material" according to present claim 14) with a strong mucosal adjuvant such as the cholera toxin B ("a polyamino acid" or "second polymeric material" according to present claims 1 and 14 respectively) subunit. Thus, intranasal administration of poly-lactic microsphere co-encapsulated ("carrier" or "microsphere comprises poly-(L-lactide)" according to present claims 1 and 10) Yersinia pestis subunits confers protection from pneumonic plague in the mouse.

Claims 1-3, 5-8, 10, 12 are anticipated by D10. D10 (abstract) describes induction of immune responses after inoculation of poly(L)lactide microspheres ("carrier" or "microsphere comprises poly-(L-lactide)" according to present claims 1 and 10) containing the V antigen ("biologically active agent" according to present claim 1) of Yersinia pestis and IFN- γ ("a polyamino acid" according to present claim 1). This led to antigen specific immune responses.

Claim 1 differs from D7 in that it describes a pharmaceutical composition comprising the components mentioned under (i), (ii), (iii).

- 3.3 The subject matter of claims 9 and 11 is not disclosed in the prior art documents and is therefore novel.
4. Inventive Step (Article 33(3) PCT).

Dependent claims 9 and 11 do not contain any features which, in combination with the features of claim 1 to which they refer, meet the requirements of the PCT in respect of inventive step, since they are mere alternatives from which the skilled person would choose, without resulting in any unexpected effect whatsoever.

5. The passages in claim 15 "a method of protecting a mammal against infection, which method comprises administration of a composition.." and "the use of a chemical...as an immunostimulant" in claim 24 are considered to cover treatment by therapy and therefore are *in vivo* methods of treatment. Moreover, claim 25 is formulated as a second medical use claim.

For the assessment of the present claims 15-17, 24 and 25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VII

6. Claim 13 is not grouped to claim 2 to which it refers and this contravenes Rule 6.4(c) PCT.
7. The references to the Figures on page 17, lines 11 and 29 of the description do not correspond to the Figures.

SECTION VIII

8. The applicant attributes to the term "biologically active agent" a special meaning, which was not generally known in the technical field concerned at the relevant filing date and contravenes the requirement that the meaning needs to be clear from the wording of the claim alone (the Guidelines C-III 4.2, Article 6 PCT).

Preferred compositions of the inventions are vaccine compositions. Thus, in a further aspect, the invention provides a method of protecting a mammal against infection, which method comprises administration of a vaccine composition as described
5 above in particular to a mucosal surface, such as a nasal surface, of a mammal.

The applicants have demonstrated that it is possible to protect experimental animals from inhalation challenge with various
10 pathogens including diphtheria, tetanus and *Y. pestis* through i.n. administration of a combined sub-unit vaccine. The adjuvantisation of these sub-units is advantageous in increasing the immune response as is microencapsulation of the sub-units in accordance with the invention. The high molecular weight
15 polymer utilised in the compositions of the invention appears to be particularly well suited to intra-nasal delivery.

In a further aspect, the invention provides the use of an adjuvant chemical as defined above as an immunostimulant in the
20 production of a vaccine for use in prophylactic or therapeutic treatment.

The invention will now be particularly described by way of example with reference to the accompanying drawings in which:
25

Figures 1 illustrates the specific serum antibody responses following a single nasal application of 1µg V and 5µg F1 antigens of *Yersinia pestis* in compositions according to the invention:
30

Figures 2-4 illustrates the immune response to nasally delivered tetanus toxoid (TT) using compositions according to the invention where BS is glycodeoxycholic acid, CYC is dimethyl β cyclodextrin, and VET is Vitamin E TPGS and PO is polyornithine;
35

Claims

1. A pharmaceutical composition comprising

(i) a biologically active agent;

5 (ii) an adjuvant chemical which increases the effect of the biologically active agent, said chemical selected from one or more of:

A) a polyamino acid,

B) a vitamin or vitamin derivative,

10 C) cationic pluronics,

D) a clathrate,

E) a complexing agent,

F) cetrimides;

G) an S-layer protein; or

15 H) Methyl-glucamine

(iii) a pharmaceutically acceptable carrier or diluent, provided that when the chemical (ii) above is selected from D) or E), the biologically active agent is an agent which is capable of generating a protective immune response in an animal
20 to which it is administered.

2. A composition according to claim 1 wherein biologically active agent is an agent that is capable of generating a protective immune response in an animal to which it is
25 administered.

3. A composition according to claim 1 or claim 2 wherein the said adjuvant chemical can act as an immunostimulant.

30 4. A composition according to any one of the preceding claims wherein the said adjuvant chemical is selected from one or more of;

A) poly-ornithine, for example of molecular weight from 5 to 150kDa;

35 B) vitamins or vitamin derivatives such as vitamin E TPGS (d-alpha tocophenyl polyethylene glycol 1000 succinate),

C) cationic pluronics which are block copolymers or surfactants which are positively charged, in particular with NH_2^+ groups

D) complexing agents which form complexes with fatty acids such as deoxycholic acid, or

5 E) cyclodextrins and their derivatives such as dimethyl β cyclodextrin.

5. A composition according to any one of the preceding claims wherein the carrier comprises a particle.

10

6. A composition according to claim 5 wherein the particle is a microsphere or liposome.

7. A composition according to claim 6 which comprises a
15 microsphere.

8. A composition according to claim 7 wherein the microsphere is prepared using a high molecular weight polymer.

20 9. A composition according to claim 8 wherein the polymer has a molecular weight of 100kDa or more.

10. A composition according to any one of claims 7 to 9 wherein the microsphere comprises poly-(L-lactide).

25

11. A composition according to any one of the preceding claims wherein the ratio of the chemical (ii) to the carrier is from 99:1 to 9:1 w/w.

30 12. A composition according to any one of the preceding claims which is adapted for administration to a mucosal surface or is suitable for parenteral administration.

13. A composition according to claim 2 which further comprises
35 a further adjuvant.

14. A method of producing a prophylactic or therapeutic vaccine, which method comprises encapsulating a polypeptide which is capable of producing a protective immune response in a first polymeric material which has a high molecular weight, in the presence of a second polymeric material which increases the biological effect of the composition.

15. A method of protecting a mammal against infection, which method comprises administration of a composition according to any one of claims 1 to 13 to a mammal.

16. A method according to claim 15 wherein the composition is applied to a mucosal surface.

17. A method according to claim 16 wherein the mucosal surface comprises an intranasal surface.

18. A microsphere comprising an S-layer protein.

19. A microsphere according to claim 18 wherein said S-layer protein is coated on the surface of the microsphere.

20. A microsphere according to claim 18 or claim 19 which further comprises an agent that is capable of generating a protective immune response in an animal to which it is administered.

21. A microsphere according to claim 20 wherein one or more of said agents are linked to the S-layer protein.

22. A pharmaceutical composition comprising a microsphere according to any one of claims 19 to 22.

23. A pharmaceutical composition according to claim 22 wherein said composition is a vaccine, intended to produce a protective

immune response against a bacterium, and said S-layer protein is derived from said bacterium.

24. The use of a chemical selected from

- 5 A) a polyamino acid,
- B) a vitamin or vitamin derivative,
- C) cationic pluronics,
- D) a clathrate,
- E) a complexing agent,
- 10 F) cetrinides;
- G) an S-layer protein; or
- H) Methyl-glucamine

as an immunostimulant.

15 25. The use of an adjuvant chemical selected from

- A) a polyamino acid,
- B) a vitamin or vitamin derivative,
- C) cationic pluronics,
- D) a clathrate,
- 20 E) a complexing agent,
- F) cetrinides;
- G) an S-layer protein; or
- H) Methyl-glucamine

as an immunostimulant in the production of a vaccine for use in
25 prophylactic or therapeutic treatment.